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Risk of autism in the use of assisted reproduction techniques: *An analysis from the Transcurssive Logic*

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ABSTRACT

This paper investigates the existence of a relationship between assisted reproductive technology (ART), such as intracytoplasmic sperm injection (ICSI) and the birth of autistic children. Based on abundant bibliography (Danan et al, 1999; Cummins, 2000; Riva & Giorgi, 2000; Palmen, 2004; Allen, 2005; Tavano et al, 2007; Palmieri & Persico, 2010; Bolduc et al., 2011, 2012; Stoodley et al., 2012; Konopka, 2013; Lyall et al, 2013; Sandin et al, 2013; Chen et al., 2015; Fountain et al., 2015; Siddiqui et al., 2016; Punamäki et al, 2016; Liu et al, 2017; Babinská et al, 2017; Griffiths & Levy, 2017; Liang et al., 2017) propose that the possibility of transference of paternal mitochondrial DNA through these techniques is a determining factor to be taken into account in the alteration of Ca^{++} homeostasis that has been detected in some autistic patients. This condition would facilitate, according to the theory of psychic functioning (Salatino, 2013, 2016), the cancellation of low frequencies (20 Hz) in the brain, which manage the sociocultural system. If we add to this the decrease in the cerebellar Purkinje cells that are usually found in patients with autism, it would explain the alterations of the psychic structure and function that produce deterioration or lack of language and social treatment shown by these patients. Taking Hempel's nomological-deductive method as a guide and complementing it with transcurssive logic, a reasonable explanation can be given to the following hypothetical case: after the use of the ICSI technique, an autistic child was born. Since this technique gives the possibility that part of the paternal mitochondrial DNA, contained in the sperm, passes to the ovule upon fertilization, and produce a case de paternal heteroplasmy. By reviewing the aforementioned etiological aspects, we were able to predict the appearance of the psychic disorders of these children, taking into account structural and functional aspects of the psychic apparatus, with firm neurobiological bases. The hypothetical case analyzed justifies paternal heteroplasmy as one of the possible causes of autism, according to some of the statistics presented by other authors.

Keyword: autism spectrum disorder (ASD), assisted reproduction techniques, psychic disorders, scientific explanation, transcurssive logic.

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1.0 INTRODUCTION

Autism is a disorder of neuropsychic development that with a practical purpose, we will characterize only through two of its relevant clinical aspects: lack of language development and lack of social functioning leads, in addition to a deterioration of the socio-communicative behavior, to the appearance of repetitive and restrictive behaviors (Konopka, 2013).

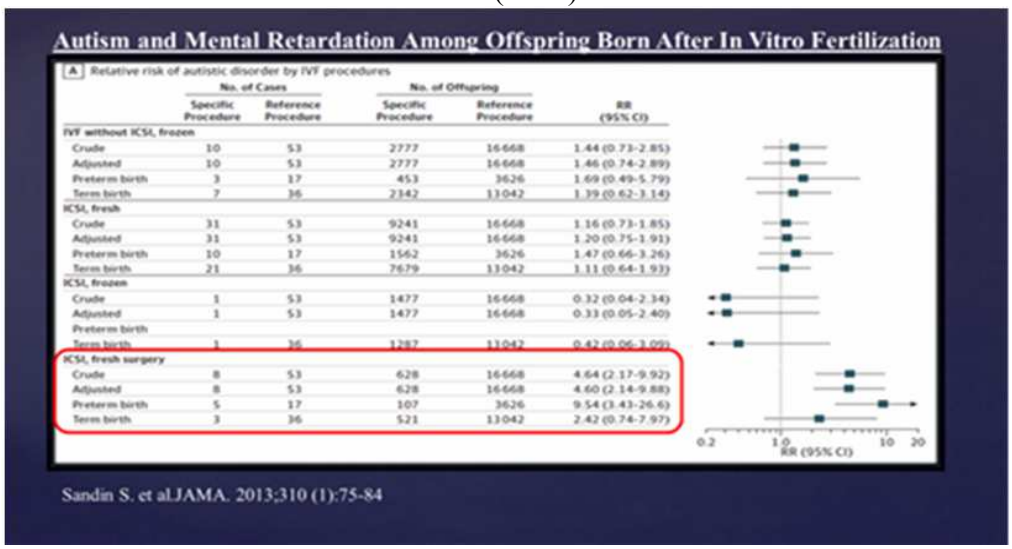
From a specific theory of psychic structure and functioning (Salatino, 2013, 2016), the previous findings can be explained. This theory proposes that the psychic apparatus is responsible for managing subjective reality, that is, the subject's own, which is constituted by three real systems: 1) *Bio-external system* (responsible for maintaining life and perpetuate it), 2) *Psycho-internal system* (which is responsible for achieving proper adaptation to the immediate environment), and 3) *Sociocultural system* (ready to adjust relationships with our peers).

In this work, we investigate the significant relationship detected between the technique of assisted reproduction of intracytoplasmic sperm injection (ICSI), among others and the birth of autistic children. We propose that the possibility of transference of paternal mitochondrial DNA (See Appendix A) through this technique, perhaps associated with failures in the mechanism of mitochondrial elimination of the ovule, is a strong determinant of the alteration in Ca ++ homeostasis that has been detected in some autistic patients. This condition would facilitate, according to the theory of psychic functioning mentioned, the cancellation of low frequencies (20 Hz) in the brain, which are the ones that manage the sociocultural system. If we add to this the decrease in the cerebellar Purkinje cells that are usually found in patients with autism, it would explain the alterations of the psychic structure and function that produce deterioration or lack of language and social treatment.

2.0 ANTECEDENTS

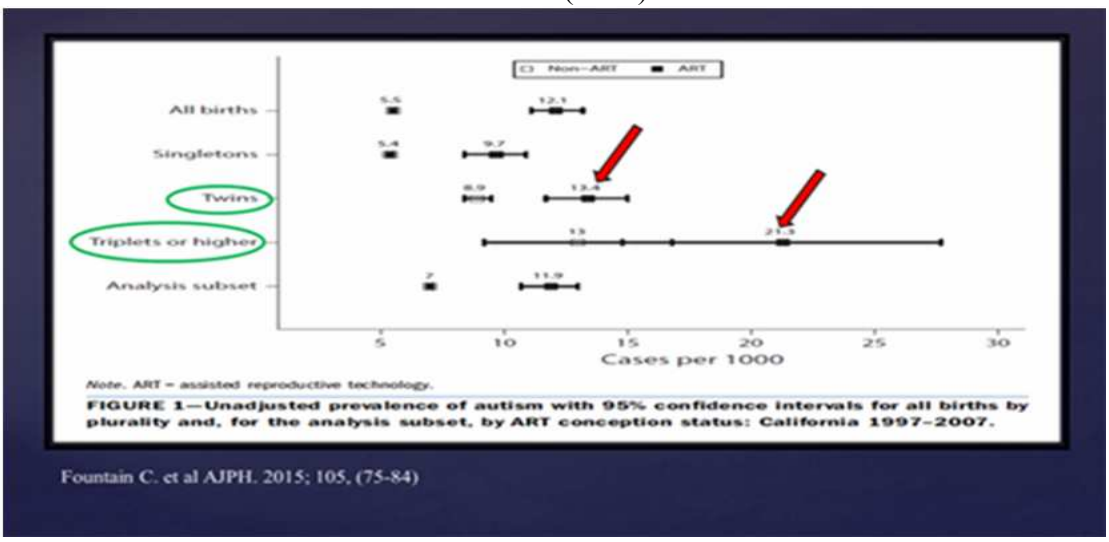
Sandin *et al.* (2013) showed that in 2.5 million children born between 1982 and 2007, 30,959 (1.2%) were conceived through IVF. In general, 103 of 6959 children (1.5%) with autistic disorder and 180 of 15,830 (1.1%) with mental retardation, were conceived by IVF. Therefore, the RR for ASD after any procedure compared to spontaneous conception was 1.14% (95% CI, 1.01-1.36: 46.3 vs. 39.8 per 100,000 persons/year). Comparing IVF without ICSI with fresh embryo transfer, there was a statistically significant increase in the risk of ASD, followed by ICSI using surgical sperm extraction and fresh embryos. (RR, 4.60 [95% CI, 2.14-9.88]; 135.7 vs. 29.3 per 100,000 persons per year). They conclude that the use of specific procedures, IVF with ICSI, for paternal infertility was associated with a small (though significant) increase in RR for ASD and mental retardation compared to IVF without ICSI. (Table I).

Table 1. Extracted and modified of Sandin *et al.* (2013)



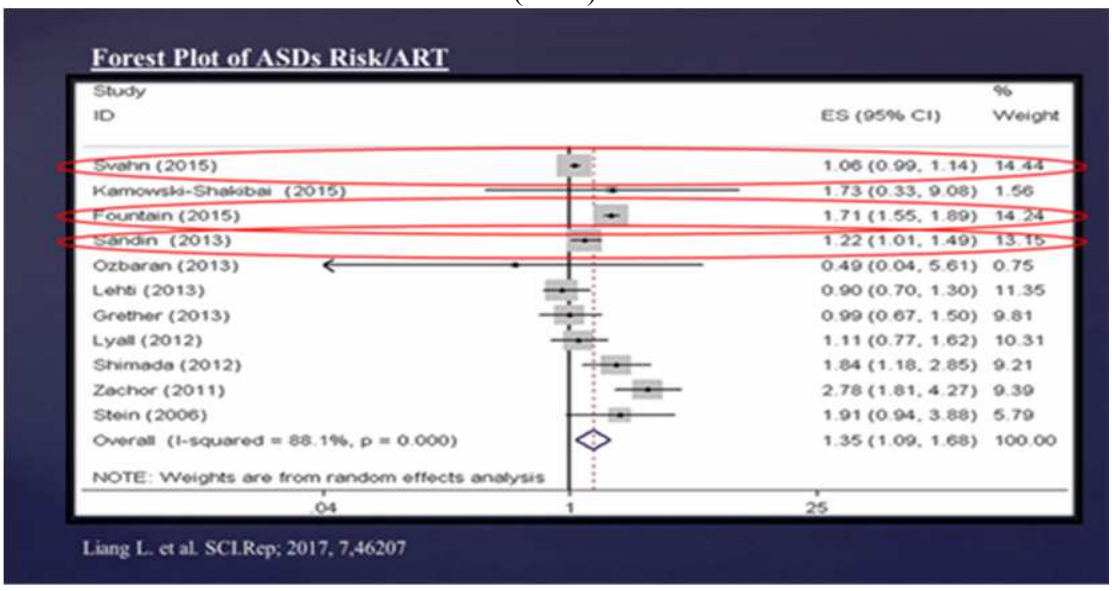
Fountain et al. (2015), studying children born in California, between 1997 and 2007, showed that in the general population, the incidence of the diagnosis of autism was double in births using ART, that in spontaneous births. This incidence was more noticeable and was directly related to the fact of multiple births (twins, triplets), something very common in cases where ART is used (Table II).

Table 2. Extracted and modified of Fountain et al. (2015)



Liang *et al.* (2017) evaluated the risk of ASD in offspring obtained through ART, in a meta-analysis. A bibliographic search was performed in PubMed, Embase, and Web of Knowledge databases until April 30, 2016, to identify all relevant records. Risk indices (RR) and 95% confidence intervals (95% CI) were calculated to analyze the strength of association by using fixed or random effects models based on the heterogeneity test in subgroup analyzes and totals. The analysis of the total of 11 registers (3 cohort studies and 8 case-control studies) revealed that the use of ART is associated with a higher percentage of ASD (RR = 1.35, 95% CI: 1.09- 1.68, P = 0.007). Also, subgroup analyzes were performed based on the study design, study location, and study quality, and some subgroups also showed a statistically significant association. This study indicated that the use of ART could be associated with an increased risk of ASD in the offspring. However, more prospective, large and high-quality studies are still required (Table III).

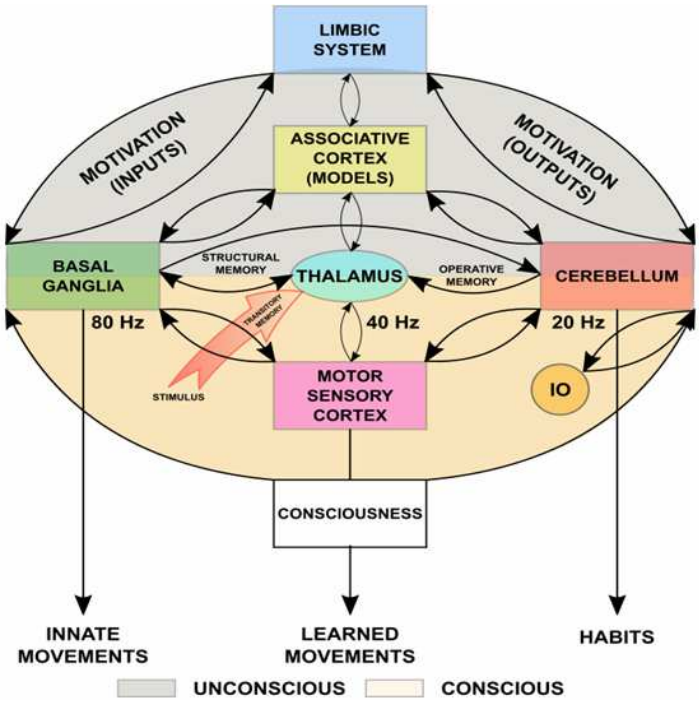
Table 3. Extracted and modified of Lian *et al.* (2017)



3.0 PSYCHIC APPARATUS

The proposed structure of the psychic apparatus is based on the anatomy, physiology, and neurobiology of the central nervous system (CNS) (Figure 1).As can be seen in the diagram, there are six gray structures of the CNS, which are involved in the constitution and management of the psychic apparatus. These structures are: 1) Thalamus, 2) Basal ganglia, 3) Limbic system, 4) Cerebral cortex (associative and sensorimotor), 5) Cerebellum, and 6) Inferior olive (IO).The stimuli that arrive, both from the social environment (socio-cultural system), as well as from the immediate environment (psycho-internal system) and even from the organism itself (bio-external system), enter through the sensory pathways, to the thalamus (set of gray nuclei) , located in the center of the brain mass). From there, they are derived to the basal ganglia (a group of gray nuclei that are at the base of the brain) that are responsible for "identification" the entries. This "identification" does nothing but determine from what real system the stimulus comes, so that our psyche can elaborate the appropriate response. The input information remains momentarily, retained in the "transient memory," which is located in the cerebral cortex. If the stimuli come from the bio-external system (of our body), their solution has absolute priority; it is the basal ganglia themselves that promote the immediate response through a series of innate, unconscious movements.

Fig. 1. Neurobiological fundamentals of the psychic apparatus



On the other hand, if the stimuli come from the immediate environment (psycho-internal system) or the social environment (sociocultural system), the basal ganglia, together with the limbic system (arranged around the corpus callosum, the structure that connects both hemispheres), they give the motivational framework to the entrance. Although the basal ganglia are what determine whether the new stimuli are "known" or not. When we already "know" the answer, that is, when we have already made a "habit" of responding in the same way to the same requirements, the basal ganglia "consult" the associative cerebral cortex (prefrontal cortex, located fore of the sensorimotor cortex).), to see if there is an antecedent of this situation. If this antecedent exists, they give the

order to execute the known motor response. This "anticipated response" is "recorded" in the cortex of the cerebellum (posterior part of the brain), which we know as "operative memory."

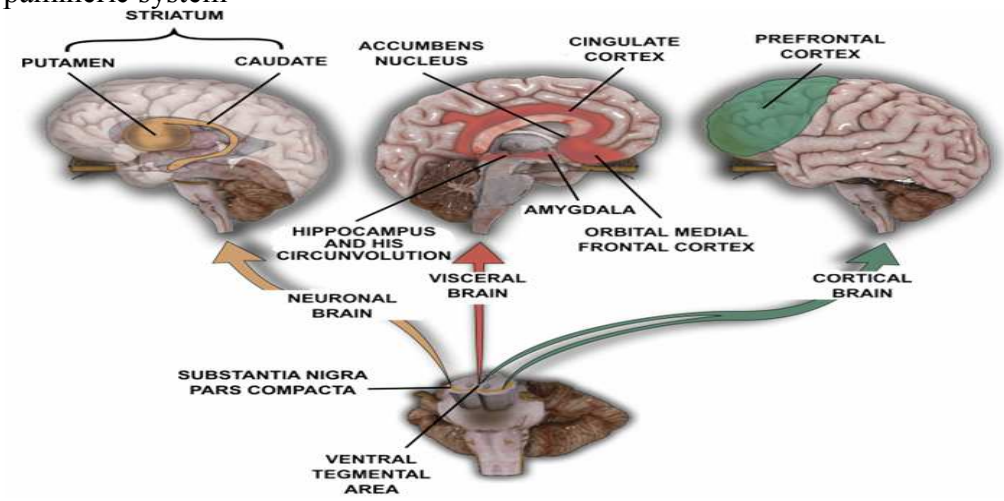
Something very different happens when the challenge posed by incoming stimuli has no antecedents. Consciousness is involved for the first time since it is a new situation, of which we must have an apprenticeship, some experience. On this occasion, the stimuli received by the thalamus are derived to the basal ganglia for their "identification" and their "classification" (process that we will deal with in detail, later), once it is verified that there is no history of the present situation, the limbic system assigns an important emotional charge, because it is unknown. Produced the "classification" of the stimuli, which indicates to the psychic apparatus the relevance of the aspects that determine the real fact perceived, according to their order of precedence, are sent to the thalamocortical circuit (thalamus-associative cortex). This circuit is responsible, in the first place, for temporarily "contextualizing" the perceptive act. This meticulous process is carried out by the specific nuclei (that contemplate what comes from outside the psyche) and the non-specific nuclei (which do the same with what emerges from the subject) of the thalamus. In the second place, the thalamocortical circuit records the fact of having learned, and, therefore, of having achieved a certain knowledge and an understanding of the new reality, will become part of the "psychic structure" of the subject. This "structure" will be housed in the "structural memory," that, which residing in the cerebral cortex, is indelible and unconscious.

When the registration of a new event was confirmed, the basal ganglia, the limbic system, the cerebellum and the inferior olive (gray nucleus belonging to the medulla oblongata, which is located at the upper end of the spinal cord), combine the corresponding adaptive response, with the due emotional tenor. This response or these "learned movements," at least in the first times they occur, are of a conscious nature. Then, if they are repeated often and successfully, they will become part of a habit that is of unconscious nature.

4.0 IDENTIFICATION AND CLASSIFICATION OF STIMULUS

Phylogenetic evidence shows us a CNS with a tripartite neuroanatomical architecture related to the organization of behavior (movement and other behaviors) (Salatino, 2012) (Figure 2). According to evolutionary antiquity, and only for didactic purposes, we can identify each of these parts as 1) neuronal brain where the psychic structure depends only on the functioning of the neurons and the structures that support it are the brainstem (formed by the midbrain, the pons and the medulla oblongata) and the basal ganglia; 2) visceral brain that sits in the limbic system that are the neural networks from which arise the affections that structure the psyche; and 3) cortical brain whose sustenance is the cerebral cortex in its maximum development degree which allows the human being, and only him, to achieve a psychic structure (neuronal arrangements) that enable the management of the cognitive phenomenon as the supreme manifestation of his subjectivity.

Fig. 2. Dopamineric system

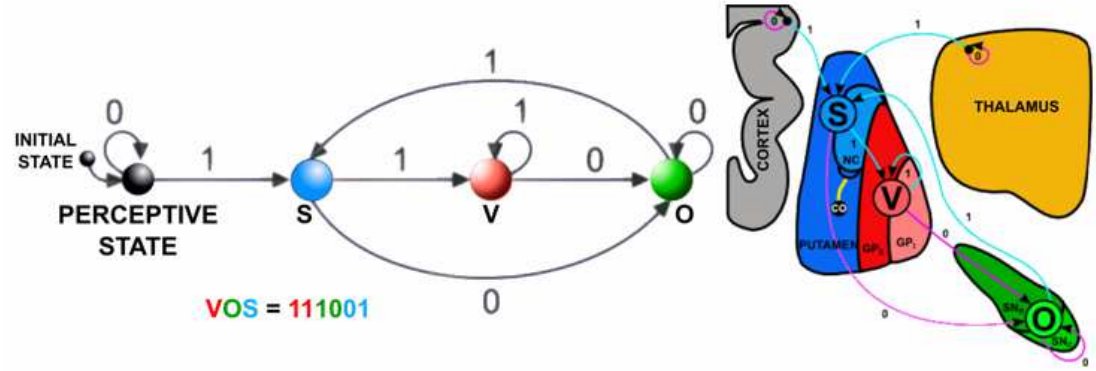


Dopamine is a neurotransmitter that is present in different areas of the CNS and is very important in the regulation of the motor activity of the organism, that is, in the projection of the response in cognition, in motivation, in milk production, in sleep, in humor, in attention, and in learning. In other words, it is dopamine that puts into function the different strata of the psychic structure described according to the real system (Salatino, 2009) that must be attended to; that is, the biological or bio-external (neuronal brain), the psychic or psycho-internal (visceral brain), or the sociocultural (cortical brain).

Dopamine is what defines, what structures are part of each of these 'evolutionary brains', but the intimate mechanism that allows the selection of one of them according to the real system to which attention has to be paid is of a nature temporary, since each one is guided by a "neurological pacemaker". The three pacemakers have a base frequency that identifies them, as follows: the pacemaker of the basal ganglia (perception) oscillates at approximately 80 Hz, the thalamocortical pacemaker (psychic structure) at 40 Hz and the olivocerebellar pacemaker (movement) at approximately 20 Hz The Ca ++ ion is the main determinant of these frequency bands.

On the other hand, for the "classification" of the stimuli, we propose a supposed perceptual unit based on the logical mechanism of a "finite automaton" (Figure 3). From the Transcurssive Logic (TL) we characterize, in a very general way, a real event like the concurrence of a subject (S = 01), an object (O = 10) and a transformation (V = 11) that binds them. The composition of this detector is very simple. It consists of an "identifier" for each of the "elements" that makes up a real event and a series of connectors, which, when interpreting its binary code, allows the system to change its status.

Fig. 3. Deterministic finite automaton – generic perceptive apparatus



References: NC: caudate nucleus - CO: cholinergic interneuron - GA: GABAergic interneuron GP_E: external globus pallidus - GP_I: internal globus pallidus - SN_R: Pars reticulata substantiae nigrae SN_c: Pars compacta substantiae nigrae - 1: activation - 0: inhibition - S: subject - O: object; V: transformation

The "perceptive machine" above can identify any of the six patterns that are formed with the three elements indicated. That is, SVO, VOS, OSV, SOV, OVS, and VSO. To identify to which real system belongs the "fact" we perceive, we use the first element of the "chain." For example, the VOS pattern that is placed in the previous figure comes from the real sociocultural system. Equivalently, if the pattern begins with "S," the phenomenon to be analyzed comes from the psycho-internal system or from what has to do with the subjectivity of living beings. Whereas if the first element is "O," it is telling us that the real fact has to do directly with our body, or with something external to us, but that it has no life.

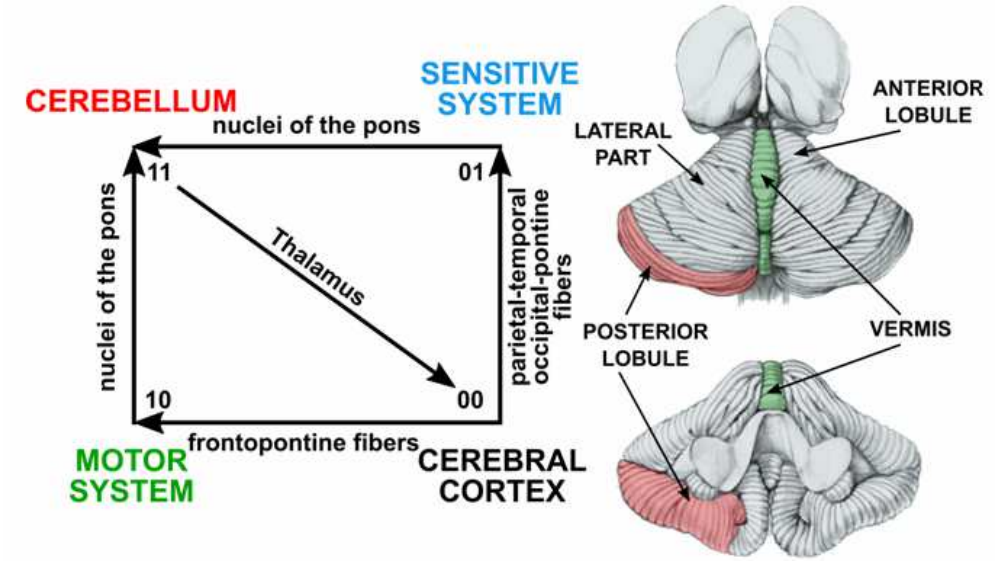
Once the origin, or the system to which the stimulus belongs, is identified, we must "classify" it. The latter is achieved by identifying the elements that follow the first. In the case of the example of the figure, the fact is identified as coming from the sociocultural system (a transformation) and prioritizes the "object" that was the destination of that transformation, rather

than the "subject" that was its producer. In the same way, we proceed with the remaining five patterns. In the same figure, we can see the "center of operations" of the perceptual system, represented by the basal ganglia, where the finite automaton has been superimposed. In the scheme, the activating (1) and inhibitory (0) connections between them and with the thalamus and the cerebral cortex have been respected (Salatino, 2014, p.42).

5.0 AUTISM NEUROBIOLOGY

From the neurological point of view, in general, autism is seen as a disorder of connectivity between different parts of the CNS. The cerebellum is at the crossroads between the sensory and motor systems, so it is essential for communication between both (Figure 4).

Fig. 4. PAU of the cerebro-cerebellar loop



The PAU of Figure 4 shows the anatomical connections of the cerebellum to the brain through the thalamus. We see that the cerebral cortex is connected to the motor system, using the frontopontine fibers while it does with the sensitive system, through the parietal-temporal-occipital pontine fibers. In turn, both systems are connected to the cerebellum through the nuclei of the pons. The cerebellar-cerebellar loop is closed using the thalamus (Becker & Stoodley, 2013, p.4). Although the cerebellum is one of the first structures of the human brain to develop, it is not fully mature until after the first postnatal years (Ibídem, p.5). This is essential to explain why "conventional language" begins to develop after 18 months (Salatino, 2012, p 245). There are important investigations that relate the malformations of cerebellar vermis (🔴) with autism (Bolduc *et al.*, 2011, 2012; Tavano *et al.*, 2007). While malformations of the cerebellar lobes are associated with selective deficits of the executing function, for example, language or "spatial cognition." The latter is very important because it reflects the patterns of cerebellar connectivity. Language difficulties are associated with lesions of the posterolateral lobule (🟢) (Riva & Giorgi, 2000; Stoodley *et al.,* 2012). In addition to the cerebellum, in autism are involved: the cerebral cortex, the thalamus and the striatum (basal ganglia).

5.1. HYSTOPATHOLOGICAL AND FUNCTIONAL CHANGES

The most consistent of the histological changes found in autism cases is the loss of cerebellar Purkinje cells, particularly from the lobes. (Allen, 2005; Palmen, 2004). A reduction in cerebellar activity (such as that found in autism) is accompanied by an increase in the activity of the cerebral cortex, in particular, of the prefrontal regions (Mostofsky et al., 2009; Takarae *et al.*, 2007). It suggests that the autistic "psychic problem" is not only structural, as we believed, but also

functional. In other words, it may have basic patterns of behavior, but, socially, it cannot project them into adequate conduct.

The interruption of GABAergic inhibition in Purkinje cells can influence the functioning in thalamocortical circuits. It has been suggested that the reduced function of Purkinje cells produces reduced cerebellar modulation of dopamine release in the medial prefrontal cortex (Rogers *et al*., 2013). It is possible that the loss of Purkinje cells ultimately leads to an imbalance of the excitation/inhibition ratio in the cortex, which is hypothesized to be an underlying mechanism of ASD (Maloney, 2013).

6.0 PSYCHIC ALTERATIONS

The most important manifestations that characterize the autistic child do not derive from pathology in itself but a different psychic disposition. The autistic psyche presents, as seen by the Transcursive Logic, marked modifications concerning what we have proposed above as a standard psyche. Such modifications, at least in the case presented in this work, are of genetic origin and, therefore, congenital.

The autistic child, literally, "lives in another world." Another is the subjective reality that sustains it, others and very different are its vital and different priorities will be then, the contributions required from the surrounding environment.

For the autistic, the social world either does not exist or if it exists it is only a rudiment that cannot be accessed because it lacks the possibility of using conventional language appropriately.

Aid programs established as suitable to deal with these children should contemplate at their base: social reintegration techniques structured on their real needs and not, like most of them, trying to 'provide' supposed pragmatic solutions for the correct use of language and in a derivative way, a "better structuring" of their thinking. The latter respond to the prejudices on which the cognitive sciences are based, which are the current frame of reference for most of the institutions dedicated to helping autistic people.

Therefore, we will not consider the alleged role of cognitions in information processing, nor will we adhere to one of the major axioms of cognitive science, which states: cognitive processes (ideas, beliefs, rules). They translate external and internal events into representations or structures of meaning (Chappa, 2003, p.98).

In this work, we are going to show a possible origin of the autistic "asociality," to call it in some way. To be more precise, an autistic person is not "asocial," in the strict sense since "asocial" is an individual (or social subject) who does not identify himself consciously or intentionally with the social group in which he is immersed. The autistic, on the other hand, never becomes an individual, that is, never becomes a social subject. His individuality is pure subjectivity, and as such, it has no possibility of identification with his group.

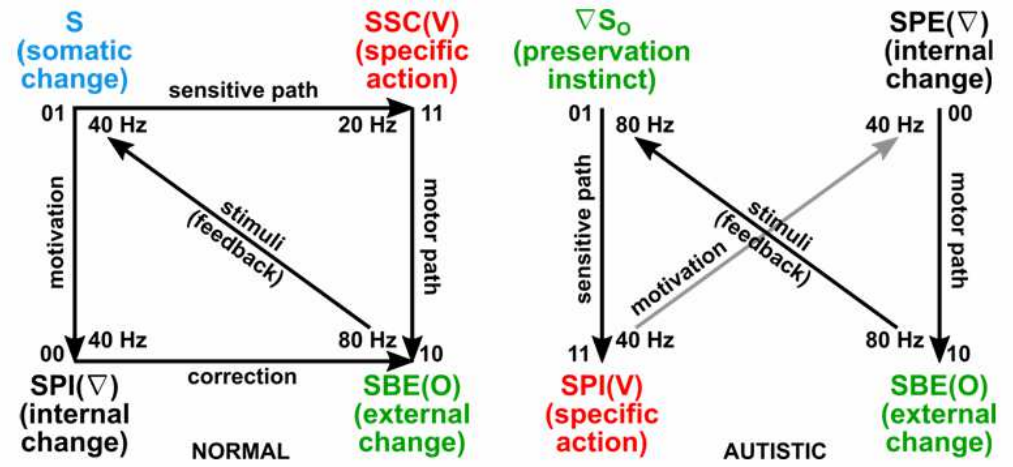
An autistic person also does not suffer from *anomie* (See Appendix B), that is, from inappropriate social behavior due to not observing the established norms. For the autistic, social norms lack meaning and the true reason for this; we should look for it in the causes that leads to its apparent 'affective anesthesia' since affection is the only socializing means of the human being.

As we have already seen in another work (Salatino, 2012), at the fundamental level, psychic structuring is based on the administration of change. The marked resistance to change evidenced by all children with autistic disorders is well known. Since we have proposed that the psyche of the autistic is not abnormal but different, it is clear then that the change is not what relates subject and object in his psyche. A direct consequence of the above is its manifest difficulty in learning the sociocultural norms that are arranged according to the dominant majority. That is, it is not possible to characterize the changes that beset his psyche. Then, the key is to be able to determine what binds the basic constituents of your psyche, that is, subject and object. Or better yet are the elements that structure your psyche subject and object? Or do you only handle related objects not because of the change, but because of the static ligatures perceived between them in the first instance? If this

were so, obviously their PAUs should have another provision and not to mention their structural and operative memories.

Let's start with the psychic PAU. It is evident that by not acknowledging the external change given its apparent perceptual indifference, the only manifestation that promotes the evolution of the psychic structure is the internal change. To clarify the above, let's see Figure 5.

Fig. 5. PAU of the autistic Psyche



References: S: subject – O: object – V: apparent transformation - ∇: non-apparent transformation. SBE: bio-external system – SSC: sociocultural system – SPI: psycho-internal system. SPE: psycho-external system - ∇SO: objective subject

In the left part of Figure 5, in a structural PAU, we see the differentiation of the original change that structure, usually, the psyche. The relationship between a somatic change (01) that generates a vital urgency (hunger) is appreciated. An external change corrects the previous imbalance (10) (maternal contribution).

Finally, a change represented by a specific action in response to external change (11) (suction). This sequence is evident or superficial. At a deep level, there is part of the original change (internal change) (00) that fulfills the function of linking and functionalizing the other changes. It is that change that is not evident except for its unmistakable manifestations. Those that are apparently allow the alternation between the other changes or the predominance of one over another, until achieving the motivation that promotes the satisfaction of the original desire. The subjective reality then arises from the conjunction of a desire and a need that must be satisfied. In the scheme, the different real systems that "administer" the described changes have been superimposed, with their respective neurobiological activations (the different frequency ranges that we have already seen) and the different processes that connect them.

In autism, on the other hand, (Figure 5, right) it is as if the desire did not exist, that is, the memory of a satisfying experience is not shown at the superficial level (01). The voluntary, non-inherited impulse that moves to live does not arise; only an involuntary and inherited need or impulse is present, useful to preserve life (00). Given the above, the psychic PAU of the autistic is structured as follows: 1) The somatic change (01) is replaced by one of the instances in which the internal change (∇) unfolds, which becomes superficial and evident (∇So (01)). The subject (S) is replaced by an "objective subject." 2) The other instance of internal change (∇), converted into a kind of "psycho-external system" (SPE∇ (00)), replaces specific action (V), which has now become deep (SPIV (11)), and represented the specific action (V), which has now become deep (**SPIV (11)**), and represented the specific response to drive the external change, that appears as help to cover the vital need. The external change (**SBE (10)**) is not modified.

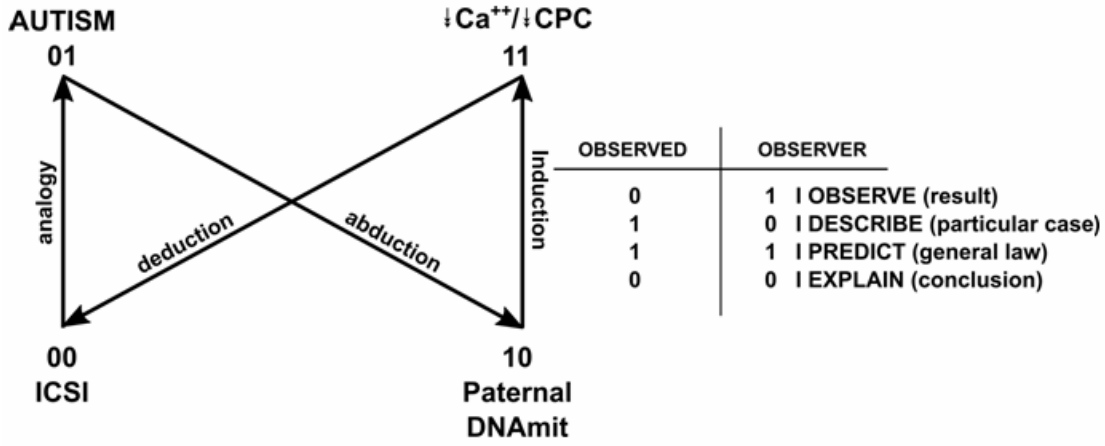
The described modifications configure a bicyclic PAU, where an internal change ends up related to an external change through another internal change. Which is equivalent to two objects related by an internal change. The first instance of internal change becomes "objective subject." The external change, the one that contributes to settle the vital need, will replace the "objective object." While the second instance of internal change will replace the specific action, acting as a means to interrelate the two previous changes, and is the one that will put into operation the reflection of suction, crying and later, more complex acts, that is, replace the objective change (**Vo**) that normally relates subject and object.

We observe in the autistic scheme the superposition of the systems that manage the proposed changes, and as can be seen, the frequency range of the 20 Hz is missing, which is the one that handles the projection of our behavior, as a conduct, to the sociocultural system and depends on the neuronal brain and the olive-cerebellar circuit. This "social disconnection" explains, in part, the clinical findings in autistics, where a kind of "inward motivation" is evident as the subject tacitly disappears.

7.0 HYPOTHESIS

Figure 6 shows the hypothetical situation in which, after the application of the ICSI technique of assisted reproduction, an autistic child is born. Assumption based on the evidence provided by several studies (Danan *et al*., 1999, Cummins, 2000, Lyall *et al*., 2013, Sandin *et al*., 2013, Punamäki *et al.,* 2016, Liu *et al.,* 2017). Assuming the possibility that part of the paternal mitochondrial DNA contained in the sperm passes to the ovule upon fertilization, given the procedure used to achieve sperm immobility (see Appendix A), I can describe the particular case. That is, it is assumed that the presence of paternal mitochondrial DNA can produce autism (Palmieri & Persico, 2010, Chen *et al*., 2015, Siddiqui et al., 2016, Babinská *et al.,* 2017, Griffiths & Levy, 2017). By invoking a universal pattern (PAU) as a general law, we can predict some structural and functional alterations of the cerebellum, such as, for example, alteration of Ca ++ homeostasis, or a significant decrease in the population of Purkinje cells in the cerebellar cortex (Riva & Giorgi, 2000, Palmen, 2004, Allen, 2005, Tavano et al, 2007, Bolduc *et al.,* 2011, 2012, Stoodley *et al*., 2012, Konopka, 2013). According to all the above, I can conclude that, in this hypothetical case, a possible explanation for the birth of a child with autistic disorder is in the use of the method of assisted fertilization ICSI or similar.

Fig. 6. Explanatory PAU



8.0 CONCLUSION

We reviewed some etiological aspects of autism, including alterations at the level of the cerebellar cortex and in the homeostasis of Ca^{++} in association with mitochondrial diseases, and made predictions about some of the supposed psychic alterations that an autistic child presents. These

psychic alterations justify the classic capital symptoms of autism, through a theory of psychic structure and function, with firm neurobiological bases. The hypothetical case of the birth of an autistic child is considered after the application of the ICSI technique of assisted reproduction, in which the generation of a mitochondrial pathology could be involved, due to heteroplasmy of paternal origin.

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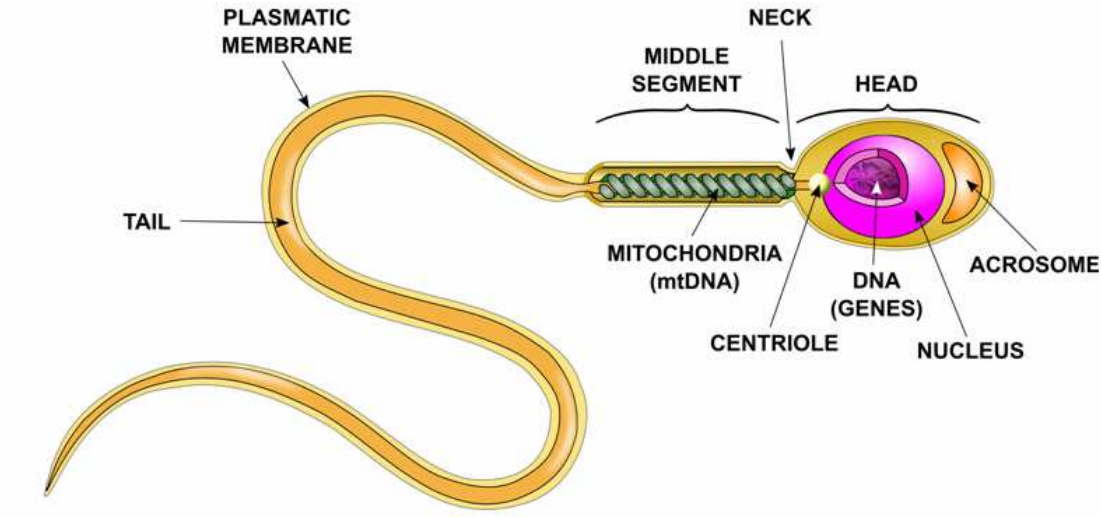
APPENDIX A
ASSISTED FERTILIZATION THROUGH INTRACYTOPLASMIC SPERM INJECTION (ICSI)

Since the successful birth of Louise Brown in 1978, in vitro fertilization has been the method of choice to treat infertility. The results obtained by the traditional technique of in vitro fertilization were inconsistent in the presence of infertility due to mild male disorders, but very poor when the malefactor was important (azoospermia, oligozoospermia, asthenozoospermia, etc.). Given these results, a new insemination technique was used: microinjection (Gardner & Simón, 2017). The first pregnancy, followed by live birth, after using ICSI was reported by Palermo in 1992. There are other indications for the use of ICSI, when the malefactor is not at stake, for example, previous failure of an in vitro fertilization, immature oocytes, etc. (Palermo, 2018).



The spermatozoon is the haploid cell (with 23 chromosomes) that constitutes the male gamete. In human fertilization, is who gives sex to the egg or zygote. They are pyriform cells composed of three parts: 1) Head, 2) Middle segment, and 3) The flagellum or tail, which gives it its mobility. In turn, the head contains two parts: the acrosome formed by enzymes that favor the rupture of the zona pellucida surrounding the ovule, to achieve fertilization. And the nucleus, which contains its genetic load in the DNA divided into 23 genes. Once the acrosome opens the zona pellucida of the ovule, the nucleus is the only part of the sperm that penetrates its cytoplasm to fuse with its nucleus and form the diploid cell (with 46 chromosomes) that represents the zygote.

As for the middle segment, it is a zone of 4 or 5 μm in length that has a large number of mitochondria (mitochondrial DNA), which give the centriole energy to move the tail and thus can progress through the neck, the uterus, and the fallopian tubes until reaching the ovule to fertilize it (Jiménez & Merchant, 2003, p.680). The ICSI technique consists of the following stages (Palermo & Sills, 2018, p. 14):

1) Preparation of the ICSI plate: there are nine drops of the medium used for the injection, one central and eight in a radial form, covered by cultivation oil. This plate is stored at 37 ° C until use.

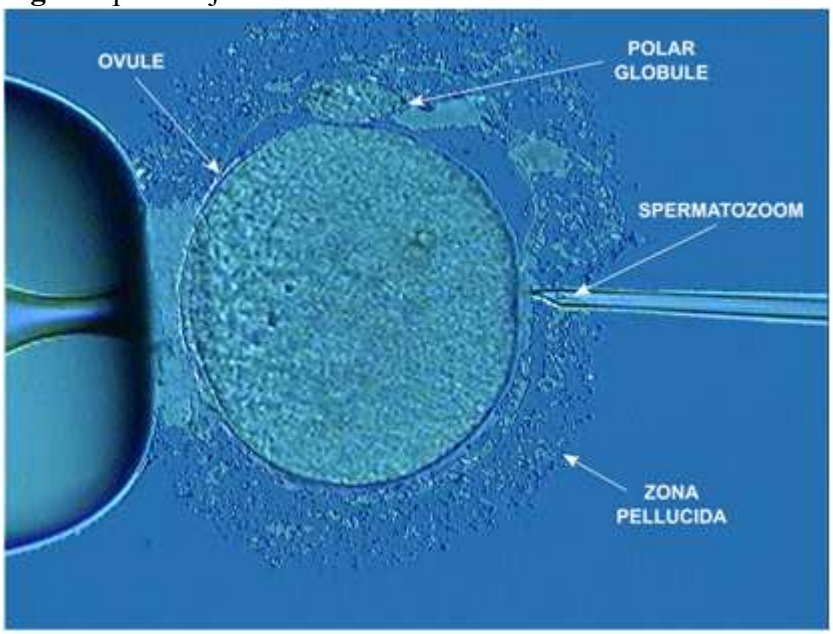
2) Loading of gametes: immediately after the injection of sperm the central drop is removed and replaced by a diluted suspension of sperm. In the other drops, the oocytes are placed.

3) Immobilization of sperm: a single sperm is selected from the drop of sperm from the ICSI dish (usually the central drop) and aspirated at the tip of the injection pipette after immobilizing it, breaking the tail by pushing it with the pipette injection against the bottom of the Petri dish. If the initial attempts at immobilization are not successful, it is repeated until the tail is twisted and broken. [It is important to note that, given the technique described, it is possible for the

mitochondria of the middle segment to enter the ovule, in addition to the nucleus, providing paternal extranuclear DNA.]

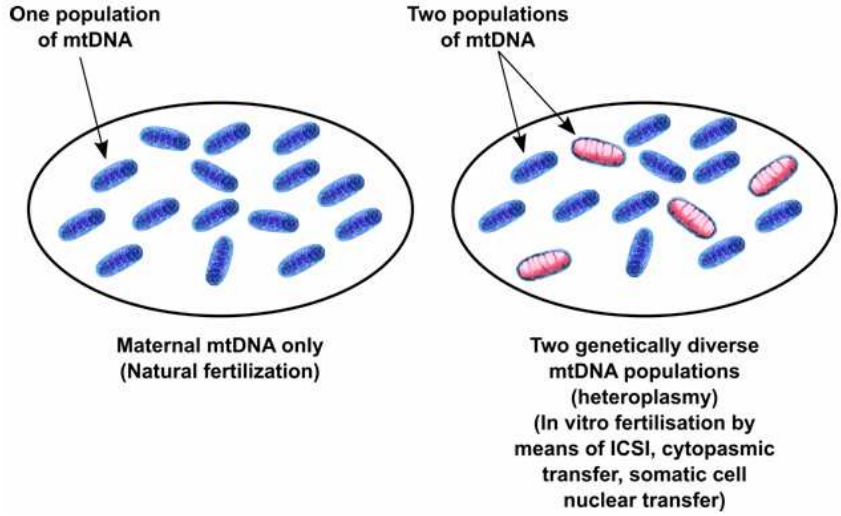
4) Sperm injection: once the oocyte is located inside the drop, it is kept in place by a retention pipette, to locate the polar body. The injection pipette focuses on the right edge in the equatorial plane at 3 o'clock. The sperm is placed near the bevel of the injection pipette. With it, is pressed at 9 o'clock until breaking the ovular membrane. Then the sperm is expelled (Figure 8).

Fig. 8. Sperm injection



HETEROPLASMY

Fig. 9. Heteroplasmy



In normal fertilization, the mitochondria of sperm origin occur in a ratio of 1: 1000 concerning the mitochondria of the oocyte, which could be the result of a dilution process (Ankel-Simons and Cummin, 1996). This assumption was incorrect since the incorporation of mitochondria in mammalian ooplasm during fertilization was demonstrated (Sutovsky *et al.,* 1996).

AUTOPHAGY

In fertilization, the mitochondria taken to the cytoplasm of the oocyte by the sperm are searched and destroyed, leaving only the mitochondria of the oocytes to propagate their mitochondrial DNA to

the offspring. This mode of clonal inheritance, the paradigm of "mitochondrial Eve" is mediated by a proteolytic resident in the oocyte.

The machinery for the degradation of proteins and organelles is based on the ubiquitination of the sperm mitochondria within the cytoplasm of the fertilized oocyte, producing autophagy.

When a lucky sperm cell fuses with the ovum, between 100 and 200 paternal mitochondria enter the ovule at the time of fertilization, which is largely surpassed by the 100,000 mitochondria derived from the mother.

In theory, as fertilization occurs, the paternal mitochondria must be destroyed. Perhaps, due to a failure of the destructive mechanism or, because the sperm comes from a testicular puncture where immature forms are taken, that destruction is not carried out.

Mitochondria inadvertently damage their own DNA through the production of free radicals of oxygen and other metabolic contaminants. This could mean a problem if the gamete uses its own mitochondria during fertilization since it could damage the mitochondrial genome that must pass to the zygote (Bromham, L. et al. 2003).

APPENDIX B

Anomie: It should not be confused with the neuropsychological disorder that affects some aphasics, characterized by the difficulty to remember the name of things.

Frontopontine fibers: are situated in the medial zone of the base of the cerebral peduncles; they arise from the cells of the frontal lobe and end in the nuclei of the pons.

Heteroplasmy: is the presence of more than one type of organellar genome (mitochondrial DNA) within a cell or individual.